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McCune–Albright syndrome and acromegaly: clinical studies and responses to treatment in five cases*

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We report here five new patients with McCune–Albright syndrome and acromegaly. In the five patients studied (three males and two females aged 18–42 years), acromegaly began before the age of 20 years and was recognized after the diagnosis of fibrous dysplasia, which was polyostotic in three cases and monostotic in two. Bone fibrous dysplasia always involved the base of the skull and in four patients prevented surgical removal of the pituitary adenoma, which was visualized easily by magnetic resonance imaging. Serum growth hormone (GH) levels ranged between 20 and 48 μg/l and were not suppressed by an oral glucose load. Thyrotropin-releasing hormone administration produced a paradoxical increase in serum GH levels in all the patients. Four of the five patients had hyperprolactinemia (43–670 μg/l). In the sole patient who could be operated on, a typical adenoma with positive immunostaining for GH was incompletely removed and postoperative radiation therapy failed to cure the acromegaly. In two patients, medical therapy with bromocriptine and/or octreotide was partially or totally ineffective whatever the dose (up to 1.5 mg per day) and duration (2–4 years) of octreotide treatment.

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The association of polyostotic fibrous dysplasia, café-au-lait skin macules and precocious puberty is known as the McCune–Albright syndrome (1, 2). This syndrome also has been associated with other hypersecretory endocrinopathies, including hyperthyroidism, hypercortisolism and acromegaly. These diverse endocrine syndromes have in common an autonomous function of cells that respond to extracellular signals through activation of the hormone-sensitive adenylate cyclase system, which catalyzes the production of cyclic AMP (cAMP). Recently, mutations within exon 8 of the Gs-α-gene that result in increased activity of the Gs protein and increased cAMP formation have been detected in affected endocrine organs of four patients with McCune–Albright syndrome (3). Moreover, these mutations were found also in tissues not classically involved in the syndrome. McCune–Albright syndromes (4–28) associated with acromegaly are rare, as less than 30 cases have been reported. Their treatment is difficult because skull involvement frequently prevents neurosurgical excision and because radiation therapy may cause bone sarcomatous transformation (17–19). We report here five additional cases of patients with acromegaly, which constitutes the largest series of such patients from a single institution.

Patients and methods

Patients

Patient 1 was a 26-year-old woman who had gradually developed classical features of acromegaly since the age of 18. Menarche was normal at 13 and she became amenorrheic at the age of 21. Diabetes mellitus was diagnosed 4 years later. She had no galactorrhea. Bone fibrous dysplasia, discovered on skull X-ray examination, remained asymptomatic until the diagnosis of acromegaly. As evidenced on the bone radionuclide images, lesions were limited to the skull. Radiographically, fronto-ethmoidal hyperostosis was associated with sphenoidal involvement. Physical examination revealed no abnormal pigmentation. Preoperative endocrine evaluation, summarized in Table 1, showed an isolated excess of GH. Computed tomography (CT) revealed an intrasellar mass. Despite fibrous dysplasia, transphenoidal surgery was possible and allowed the tumor to be removed. Histological examination of the tumour disclosed a typical pituitary adenoma. By immunocytochemistry, cells only stained for GH. Postoperative serum GH levels remained elevated and radiation therapy was undertaken. The

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Table 1. Clinical and hormonal characteristics of five patients with McCune–Albright syndrome and acromegaly.

Patient no.	Sex/age (years)	Basal serum GH (μg/l)	GH response to TRH	GH response to OGTT	IGF-I	PRL (μg/l)
1	F/26	37	Increased	No response	Not determined	10[a]
2	M/42	28	Increased	No response	58.8 IU/l[b]	670
3	M/18	38	Increased	No response	5.5 IU/l[b]	43
4	F/23	30	Increased	No response	630 μg/l[c]	104
5	M/18	48	Increased	No response	759 μg/l[c]	150

[a] Normal levels < 20 μg/l.
[b] Normal levels < 1.4 U/l.
[c] Normal levels < 250 μg/l.

patient received a total dose of 55 Gy. Endocrine evaluation 3 years later showed persistently increased serum GH levels. She was then lost for follow-up.

Some of the data for patient 2 have been reported previously (27). This patient presented to our institution at the age of 42 with severe fibrous dysplasia involving the skull and the face, which was responsible for bilateral exophthalmos and facial deformities. The disease was polyostotic: bone lesions were found at the base of the skull, frontal and temporal bone, the lumbar spine, the right rib cage and the right femur. Sexual maturation was not precocious. On physical examination, the acromegalogigantism was obvious: height was 203 cm, weight was 107 kg and, in addition to facial deformities, severe kyphosis and café-au-lait skin typical flat skin lesions with irregular margins of the right side of the neck and of the trunk were found. Hormone data at the time of admission are presented in Table 1. Hypersecretion of GH was associated with hyperprolactinemia and secondary hypogonadism (serum testosterone level 6.7 nmol/l, normal range 10.4–28 nmol/l; serum FSH and LH levels 0.8 and 5.3 IU/l, respectively). Owing to the huge facial deformities, which did not allow us to introduce the head of the patient in the tubes, it was not possible to examine the pituitary area by either CT or magnetic resonance imaging (MRI). Massive bone lesions of the base of the skull prevented surgical excision of the pituitary lesion. During plastic surgery on facial bones, fibrous dysplasia and normal bone were obtained for histological evaluation. Examination of undecalcified bone sections of normal skull showed a membranous bone covered with alkaline phosphatase-positive osteoblasts and normally deposited osteoid along the bone surface. In contrast, the dysplastic bone was characterized histologically by the deposition of a woven immature bone matrix, excessive deposition of osteoid, extensive marrow fibrosis with numerous alkaline phosphatase-positive cells and increased bone resorption. These histological findings are consistent with a high rate of bone formation and resorption in the dysplastic bone area relative to the uninvolved bone. The patient refused complementary medical therapy with a somatostatin analog and was lost to follow-up.

Patient 3 was an 18-year-old man with a history of fibrous dysplasia since the age of 6, leading to severe deformation of the left facial bones and left side of the skull and causing exophthalmos and loss of vision in the left eye. He previously had undergone neurosurgical decompression of the left optic nerve. Skull roentgenograms showed considerable dysplasia of the left frontal bone, with major thickening of the orbital roof and of the spenoidal and ethmoidal bones. No peripheral bone lesions were found. Puberty did not occur prematurely but, at the age of 16, growth accelerated and acromegalic features developed leading to the diagnosis of acromegalogigantism. At the time of admission the patient was 198 cm tall, weighted 100 kg and presented café-au-lait skin macules on the trunk typical of the disease. In vivo dynamic GH studies are presented in Table 1. Other pituitary functions were normal, except for PRL serum levels, which were increased moderately to 43.5 μg/l. Magnetic resonance imaging demonstrated an intrasellar pituitary adenoma with a right laterosellar extension. The thickening of the base of the skull prevented neurosurgery to remove the pituitary adenoma. The patient refused medical therapy with octreotide.

Patient 4 was a severely affected 23-year-old woman who had fibrous dysplasia since the age of 3. At this time progressive asymmetrical facial deformation developed, beginning with a prominence of the right maxilla. Between the ages of 11 and 13 she underwent three cosmetic operations of the face. Histological examination of bone lesions was consistent with the diagnosis of fibrous dysplasia. Dysplasia was polyostotic but predominated at the craniofacial level, with lesions involving the right maxilla and mandible, the frontal and parietal bones (which appeared thickened) as well as the right wall of the orbit. Skeletal X-ray examination demonstrated enlargement of the fifth rib and densities on vertebral bodies L2 and L3. A bone scintigram showed disseminated areas of increased uptake. Acral enlargement, weight gain, excessive perspiration and worsening of deformation began at the age of 20. Menarche occurred at the age of 12. The patient, who had been amenorrheic since the age of 21, presented with galactorrhea. Her weight was 84 kg and her

height 176 cm. Three café-au-lait skin areas of pigmentation, irregular in shape, were found on the trunk and on the left leg. The patient had diabetes mellitus, initially requiring treatment with hypoglycemic agents. Insulin therapy was initiated after severe ketoacidosis. The results of a hormonal work-up are summarized in Table 1. Moderate hyperprolactinemia was associated with the acromegaly. Computed tomography and MRI showed an intrasellar macroadenoma with a suprasellar extension displacing the optic chiasm and a laterosellar extension displacing the optic chiasm and a laterosellar extension invading the left cavernous sinus. The patient, however, did not experience visual field abnormalities. Surgical removal of the pituitary tumor was not possible, owing to the thickening of the base (Fig. 1). Medical therapy with octreotide was started at a dose of 100 μg three times daily.

In the case of patient 5, an 18-year-old man, fibrous dysplasia was discovered at the age of 9 because of a lesion of the right femur. The disease was polyostotic, involving cubitus bone and the craniofacial area with multiple lesions of the vault and the base of the skull. A rapid loss of visual acuity in the right eye due to compression of the optic nerve by bone thickening led to surgery on the right orbit. Dysplastic bone biopsy confirmed the diagnosis by showing typical lesions. Acromegaly probably began at the age of 14 and was discovered during the evaluation of gynecomastia associated with galactorrhea, before acromegalic features developed. At the age of 18 the patient's height was 181 cm and his weight was 83 kg. Severe facial deformities were present, with bulging of the forehead and lateral displacement of the orbits. Bilateral gynecomastia and galactorrhea were found on clinical examination, as well as right-sided irregular café-au-lait skin macules on the thorax and abdomen. The results of a hormonal work-up are summarized on Table 1. Excess GH was associated with hyperprolactinemia. Magnetic resonance imaging disclosed an intrasellar adenoma with an infrasellar extension. Once again it was impossible to reach the pituitary lesion by any neurosurgical approach, and medical therapy with octreotide was decided on. Treatment was started at 100 μg three times daily.

Methods

Growth hormone, IGF-I and PRL serum levels were measured using commercial kits (29, 30). Thyrotropin-releasing hormone stimulation tests were performed by injecting 250 μg of TRH; blood was drawn 30 and 15 min before injection, at the time of injection and 15, 30, 60, 90 and 120 min post-injection. Oral glucose tolerance testing (OGTT) was done by measuring GH at 0, 30, 60, 90 and 120 min after administering 100 g of glucose. The GHRH test was performed by injecting 1 μg/kg GHRH and measuring GH serum levels 15 min before and 0, 15, 30, 45, 60, 90 and 120 min after the injection. A diurnal hourly GH profile was obtained before and at regular intervals during treatment in patients 4 and 5. Reported GH serum levels are the mean of 12 values.

Results

Clinical and biochemical studies

The five patients with McCune–Albright syndrome had active acromegaly, as evidenced by high serum GH levels (20–48 μg/l), and increased IGF-I levels (Table 1). An oral glucose load did not produce a decrease in serum GH levels in any of the five patients. Thyrotropin-releasing hormone injection produced a paradoxical increase in serum GH levels in every case. The GHRH test was performed in two patients (patients 4 and 5) in whom GH serum levels increased from 21 to 93 μg/l and from 35 to 70 μg/l, respectively. The PRL serum concentrations were high in four of the five patients (43–670 μg/l). A positive response of PRL to TRH administration was present in these four patients. Hormonal features observed in our five patients were thus typical of active acromegaly.

Hormonal response to therapy

Patient 1 was the sole patient who could be operated on. Removal of a typical pituitary somatotroph adenoma reduced GH serum levels but they still remained high. Postoperative radiation therapy (55 Gy) did not cure the acromegaly, as GH serum levels remained elevated (8.4 μg/l). Surgery was impossible in the remaining four patients because of extensive parasellar fibrous dysplasia (Fig. 1).

In patient 4, octreotide therapy did not modify significantly the GH serum levels, whatever the dose (100–500 μg, sc, three times daily) or duration (up to 24 months). After 9 months of therapy with octreotide alone, PRL serum levels fell from 105 to 25.5 μg/l.

Patient 5 was treated with bromocriptine (5–15 mg per day) for 4 years. The PRL serum levels normalized during treatment but GH and IGF-I serum levels remained unchanged. Treatment with octreotide started at a daily dose of 300 μg and increased progressively to 600 μg reduced GH serum levels to 8 μg/l, but IGF-I serum levels remained elevated (between 810 and 968 μg/l). After 1 year of treatment, despite near-normalization of GH serum levels, persistently high IGF-I serum levels (above 900 μg/l) led us to increase the dose to 500 μg, sc, three times daily. One year later, 5 mg of bromocriptine was added because GH levels began to increase (18.5 then 46.8 μg/l). After 4 years of treatment with octreotide plus bromocriptine, the mean GH levels in the diurnal profile remained elevated (20 μg/l), as did IFG-I serum levels (800 μg/l). Octreotide alone did not influence PRL

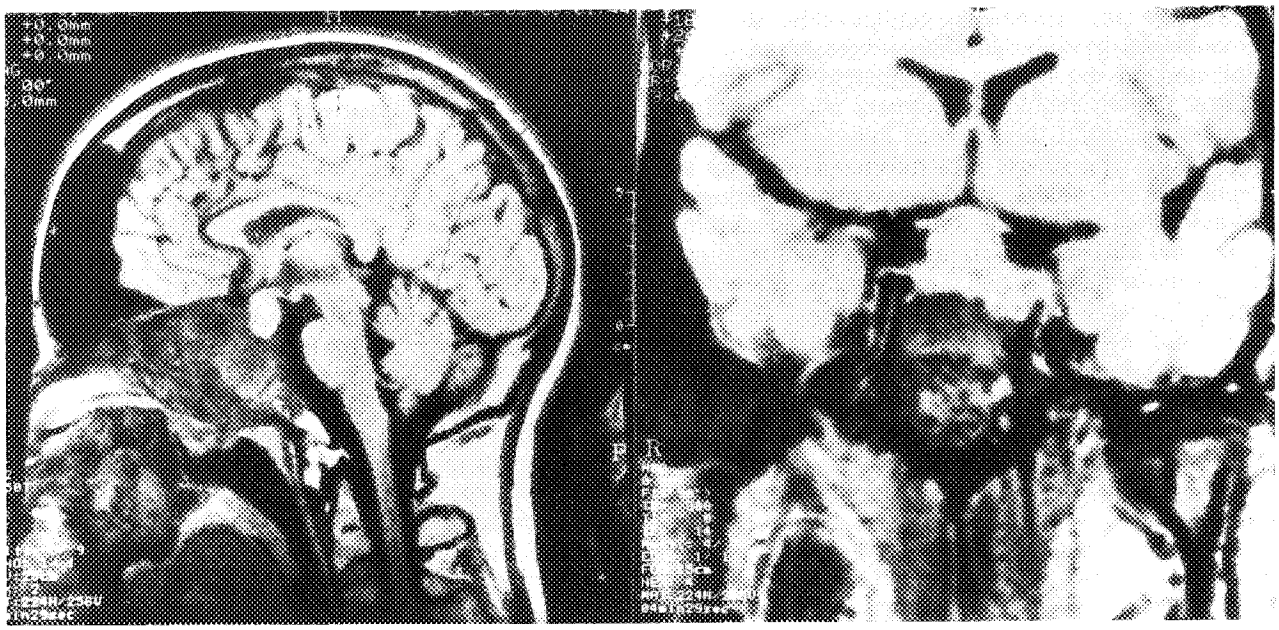

Fig. 1. Cranial magnetic resonance imaging showing an extensive bone fibrous dysplasia and a pituitary macroadenoma in a 23-year-old woman with McCune-Albright syndrome and acromegaly.

serum levels, whereas bromocriptine reduced the plasma PRL level to 22.8 μg/l. These responses to octreotide are consistent with at least partial resistance to somatostatin.

Tumoral volume during treatment

Serial evaluation by MRI did not disclose any modification in tumour mass in patients 4 and 5 during treatment with octreotide.

Discussion

This study reports on five new patients with McCune–Albright syndrome and acromegaly, placing special emphasis on hormone dynamics and therapeutics. Even if, in their first reports, McCune (1) and Albright et al. (2) described patients presenting the classic triad of precocious puberty, polyostotic fibrous dysplasia and skin pigmentation macules, it is now clear that the disease may affects other endocrine organs (such as the pituitary gland, as was the case in our patients) and may involve skin, bone or endocrine glands; the presence of at least two of the three lesions is sufficient for the diagnosis of McCune–Albright syndrome (31). Since the first description of acromegaly associated with McCune–Albright syndrome by Scurry et al. in 1964 (4), about 30 cases have been reported, including the five patients in the present series (5–28). As in the present series, patients are generally young at the onset of acromegaly; indeed, on only four reported cases did the symptoms of acromegaly appear after the age of 20 (4, 8, 18, 27, 28). In most cases acromegaly is diagnosed on the basis of growth acceleration rather than on facial dysmorphism; the latter is usually difficult to assess because of facial deformities due to fibrous dysplasia. The course of dysplastic lesions does not seem to be related to the time of onset or degree of activity of acromegalic disease. In half of the reported cases, acromegaly and/or amenorrhea–galactorrhea were the first manifestations of an endocrine disturbance associated with fibrous dysplasia. In this respect, it might be warranted to test GH secretion regularly in all patients with McCune–Albright syndrome or fibrous dysplasia. No endocrine organs other than the pituitary were involved in our five patients. This contrasts with the high prevalence of premature puberty reported in ten girls and six boys (4, 5, 8–14, 20, 22, 24, 25, 27, 28), thyrotoxicosis in four cases (20–22, 25) and hypercorticism in one (25). All but five of the patients described so far had café-au-lait skin macules, but only three (including two of our patients) had monostotic lesions. In almost every case the base of the skull was involved, and this explains the frequent delays in diagnosis because the high degree of facial deformities masks the usual features of acromegaly.

The hormonal characteristics of our patients were very similar to those described previously in McCune–Albright syndrome. Hypersecretion of GH was marked and was not suppressed by OGTT, which, by contrast, often caused a paradoxical increase in serum GH levels. The similarly paradoxical increase in serum GH levels after TRH administration in all our patients appears to be a consistent feature of McCune–Albright

syndrome associated with acromegaly, as only one reported patient (21) failed to show a paradoxical response. The increase in GH serum levels following GHRH administration in all the patients studied so far (two in our series and five in the literature) (22, 24, 25) is surprising given that the acromegaly in McCune–Albright syndrome may be due to a mutation of the Gs-α-gene that induces a permanent increase in the activity of Gs protein comparable to that obtained after binding of GHRH to its receptor on somatotroph cells. The responsiveness to GHRH observed in our patients and in a minority of acromegalic patients whose pituitary somatotropic adenoma showed the activating mutation (32) suggests that the permanent stimulation induced by the mutation may not be maximal.

The exact nature and importance of the pituitary lesion is difficult to assess, owing to the unavailability of reliable imaging methods in earlier reports and the technical problems with the examination itself (facial deformities) or with interpretation of the results (particularly on CT scans, due to bone thickening). In contrast, we found that MRI can distinguish clearly between adenomatous pituitary and fibrous bone tissue. In the combined analysis of the literature and of our series, we found evidence of a pituitary adenoma in 64% of cases. Morphological studies of the pituitary obtained at autopsy or surgery revealed either a normal pituitary (9) or evidence of a pituitary adenoma that was chromophobe (7) or eosinophilic (9, 23) or showed positive immunostaining for GH in one of our cases. A mammosomatotropic hyperplasia also was reported once (14).

As was the case in our series, thickening of the base prevents surgical removal of the pituitary adenoma in the majority of patients. As radiation therapy may cause sarcomatous transformation (17, 19), we and others (20, 22–24, 27, 28) decided to try medical therapy of acromegaly when surgery was not possible. Bromocriptine failed to reduce serum GH levels in two of our patients, as was the case in 12 other patients (12–14, 16, 18, 20, 22–24, 27). Octreotide, the long-acting somatostatin analog, produced a partial decrease in serum GH and IGF-I levels in our two treated patients but without reducing the tumor mass. In the other six reported cases (20, 22–24, 27, 28), octreotide efficiently suppressed GH hypersecretion (60–90% reduction in mean values) but levels only normalized in two cases (20, 23). In one of the latter (23), GH and IGF-I only normalized when octreotide was combined with bromocriptine. Octreotide treatment was associated with a partial shrinkage of the pituitary tumour in two cases (20, 22). Thus, the efficiency of octreotide therapy appears to vary from one patient to the next. This strongly suggests that the activating mutation, if present, does not confer a characteristic responsiveness to somatostatin. Moreover, recently we drew the same conclusion from experiments carried out in vivo and in vitro in a series of "classic" acromegalic patients presenting with or without the gsp mutation and treated with octreotide (33).

In conclusion, we report five new cases of McCune–Albright syndrome associated with acromegaly, the clinical and biochemical features of which are similar to those in previous cases. In contrast with other reports, we observed a very partial response to a somatostatin analog. As surgery often is prevented by fibrous dysplasia of the base of the skull and radiation therapy can induce sarcomatous transformation, effective treatment of GH hypersecretion remains a problem.

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